[Slide.]

To look at the incidence of events by dose, which is in the next slide, if you look specifically at ulcer complications at the two doses, very low dose and low dose aspirin, there was no apparent difference in the crude rate of events in terms of the different doses of aspirin.

There was, however, a trend towards a higher rate of the extended endpoints, symptomatic ulcers and ulcer complications in terms of more events on the higher doses of aspirin.

DR. HARRIS: Thank you. I am just going to go around the table and just ask, with respect to really the second part of the question, and basically, you know, a yes or a no.

Does there appear to be a safety signal in this database regarding concomitant use of COX-2 selective agents and aspirin?

Dr. Wolfe, yes or no?

DR. M. WOLFE: I have to say maybe, it is confusing.

DR. PINA: I would have to say maybe, but more with a trend to possible yes.

DR. NISSEN: I will say yes.

MS. McBRAIR: I will think it is confusing.

DR. WOFSY: Well, if a signal means something that

should be followed up on, I would say yes.

DR. CALLAHAN: Leigh Callahan. I would say maybe. I would like to see the additional data recommended by the statistician.

DR. HARRIS: I am going to say maybe, too.

DR. WILLIAMS: Yes.

DR. SAMPSON: Maybe.

DR. ELASHOFF: Certainly additional analyses need to be undertaken.

DR. HARRELL: If a signal means evidence, I will say no.

DR. HARRIS: Are you satisfied?

DR. DeLAP: I think I am just struggling with what I have heard there. There are a couple of different ways, I guess, that I think people may be addressing this question. One is just do we need to know more about use of the COX-2 drugs in conjunction with aspirin. That is one way of looking at the question.

Another way would be is there something that looks like there might be a unique problem with COX-2 selective drugs used in conjunction with aspirin, I mean are we actually concerned that it could be worse than, you know, just any other drug in conjunction with aspirin.

I think what I have heard from the discussion is most of the people are answering it more in the former

sense, that they just think that there is more that needs to be learned about what happens when you use these drugs together rather than that you have a concern that there is a specific, you know, something critical potentially going on here that really requires further study for that reason.

DR. HARRIS: Would it matter if one were to ask, would, as a treating rheumatologist, one feel any more comfortable giving celecoxibs with low dose aspirin as you would with another nonsteroidal?

In a patient who is taking low dose aspirin, would one want to feel better about giving celecoxib versus another nonsteroidal, would that get at it?

DR. DeLAP: Well, I think that is an interesting question, too. That is a little different question than we asked, but I am not so sure.

DR. HARRIS: It is a question I wanted to ask.

DR. DeLAP: I am not sure how to answer it, but certainly, as chair, if you want to entertain some discussion, that is your prerogative.

DR. HARRIS: Would you like to just comment briefly and then we will move on, which is, would one feel any better about recommending, in a patient taking low dose aspirin, recommending Celebrex versus another nonsteroidal?

DR. CRYOR: Very briefly, based upon prior information, I would have liked to have felt better, but

based upon the information provided to us in the CLASS trial, it doesn't support that.

DR. M. WOLFE: A point of clarification because this is driving me crazy. I would like to ask the statisticians for clarification. How do we have such different presentations this morning? I am really confused. We have, you know, one looks gold and one looks like tin, and I don't understand the differences, and I want the statisticians to explain this to me because a lot of us are saying the same thing.

We had the impression that the paradigm was correct, and now we are being told it is not correct. Does anybody else feel the same way I do? Is anybody else confused, because I am very confused?

DR. SAMPSON: Dr. Wolfe, could you clarify your confusion, are you talking about in the context of-- [laughter] -- I am confused about your confusion. I mean both presentations were well done, they had different focuses, but what specific aspect is causing that you would like us to try to expound on further?

DR. M. WOLFE: Correct me if I am wrong, but the conclusion of the sponsor was that they were able to not fulfill their primary objective by a small, you know, by 0.09 was the p-value, when the primary objective in taking out the aspirin group it became a 0.037, whereas, the

presentation by the FDA is that these drugs are the same, there is absolutely no difference.

Unless I missed something, these are two different conclusions based on the data.

DR. GOLDKIND: The FDA presentation focused on comparisons to teach of the NSAIDs, and I think the sponsor dealt with the global, as well as some specifics, but that may be part.

DR. GEIS: So, what we showed was when you did the combined endpoint, we were statistically different with the NSAIDs combined. When you separated the NSAIDs out, we were statistically superior to ibuprofen, but not to diclofenac, so we did show that.

Now, when you take aspirin out, you see the difference is even greater between Celebrex and the ibuprofen.

DR. M. WOLFE: I still have a question. When the study came to FDA, was the study to analyze celecoxib against both ibuprofen and diclofenac, or were they two separate studies, because the primary objective was to compare against two, then, we have to combine the data. If not, if they are two separate studies, we compare against each one individually.

DR. LU: I am Laura Lu, the statistical reviewer for celecoxib. I just want to clarify, clear your

confusion. You pointed out the sponsor's p-value were 0.09 and the 0.037 for the comparison between celecoxib and ibuprofen, and from our side we are saying no statistical significance was shown for the comparison because I think from our side, we are following the stepwise procedure.

First, you compare celecoxib over the combined NSAID groups, and only when there is statistical significance shown in this step, you can go down to make individual comparisons, because the first step was not passed for these comparisons, the p-value was larger than 0.05. That is why we say there is no overall statistical significance, but I think what the sponsor mentioned, 0.09 and 0.037 was that individual comparison between celecoxib and ibuprofen, so that is the second step comparison.

DR. HARRIS: Thank you, Dr. Lu.

Dr. Sampson?

DR. SAMPSON: Dr. Wolfe, let me follow up. I think Dr. Lu has given you the basic answer. The comparisons of interest were Celebrex separately to diclofenac and ibuprofen, and the sponsor, at least my interpretation--I will speak now just as a statistician reviewing this--my interpretation is the sponsor wanted a, quote, unquote, "win" if Celebrex either was superior to ibuprofen or superior to diclofenac, so that they could win in either of those two ways. They did not feel that they had to beat

both of them.

Standard statistics would require to protect the so-called type 1 error, that is, making false positive recommendation, that because you are doing two comparisons, so you could win on either one, there is one comparison. You would run both comparisons, say, at the 0.025 level, which is something that is traditionally done.

They chose, however, to use a different way to adjust for the multiple comparisons by doing an overall test first, and if that were significant, then, actually going down and doing the individual tests at the 0.05 level, and it was their view based on the--I would guess--it was their view based on their analysis that this was a more powerful procedure. It offered them a higher chance of success based on what they expected.

But the first comparison that they do of Celebrex versus so-called NSAID together, again, it is just a statistical artifice to allow them to run their second tests at the 0.05 level individually rather than having to do them as you and I might do is at the 0.025 level without a pretest.

All that being said, if you look at their primary--I have got some handwritten stuff here, so I hope I am going to quote this correctly--but if you look at their primary endpoint, the POB, the combined NSAID group had a p-

value of 0.45. That does not allow them to step down to test the either two, so in that case, they can't get significance on the comparison of Celebrex versus diclofenac or versus ibuprofen.

On the other hand, if they use PUBs, which is their secondary variable, they do clear the first step. I think I have a p-value of 0.04. That allows them then to go to the second tier test, in which case they can establish a difference based on the PUBs between Celebrex and ibuprofen because the p-value there is 0.017.

Then, when they get to the issue of aspirin and non-aspirin, leave aside that that itself is maybe a tertiary analysis, and it is not prespecified, when they do the non-aspirin--

DR. GEIS: This was prespecified, by the way.

DR. SAMPSON: When they do the non-aspirin, that is, they look at non-aspirin users, if you look at the comparison of Celebrex versus the total NSAIDs, I think I have a p-value there of 0.185, which if you were using their predescribed simultaneous, their multiple comparisons would not allow them then to step down to look at Celebrex versus diclofenac or ibuprofen if, in fact, you ignored, and don't do the overall test first, then, they get to the 0.037, and that is how they would declare for the POBs in the non-aspirin there is significance.

That is where Dr. Witter and Goldkind talked about a trend that was unadjusted for multiple comparisons. It seems to me maybe that is part of the confusion at 0.037 is how to interpret that. The sponsor uses that. The agency is telling you that you had better put a lot of qualifiers around that.

Then, there is the other issue. I still am puzzled by this, is that if you look at the people that took aspirin, and you look at the POBs with ibuprofen, without aspirin and with aspirin, you see quite an observable difference, and that is the question I was asking Dr. Witter and Dr. Goldkind to try to explain that, that at least to the observed rates, and this is not any significance, if you take ibuprofen and add aspirin to that, you get a lower, dramatically lower POB rate.

This is this, what they call the reverse trend, and I was hoping that you might be able to explain that confusion to me. I am sorry for such a long answer. I hope that helped clarify it.

DR. HARRIS: Dr. Elashoff.

DR. ELASHOFF: Just one additional comment. Although it was planned to look as a secondary analysis at the influence of risk factors like aspirin, they looked at multiple other risk factors, and aspirin is the only one with a significant interaction, which is why they broke it

down, but if you were going to make any kind of p-value adjustment for the--I don't know whether it is five others or six others, or something like that--then, you might not even ever end up, well, you wouldn't ever end up looking at that interaction at all.

So, there is another level of multiple comparison which no adjustment was made for.

DR. HARRIS: Before we go on, could I just ask from the perspective of the FDA, is there anything else in terms of the interpretations given so far? This is with respect to the comments made by Dr. Sampson or Dr. Elashoff.

DR. GOLDKIND: Not really an additional comment. I would agree with that, I guess the only additional comment that we would have to make, and I think it was in the reviews, is that it was an advantage in terms of a public health study to include those patients with aspirin, so that while statistically, it presents a problem, it scientifically was to be--obviously, there is biological plausibility to look at the groups which again you would have to I think add into the mixture of how rigorous one looks at the issue of the need to statistically correct and how far someone would be willing to go with the data as it is uncorrected.

In a very purist sense, we probably wouldn't be having a lot of this discussion, we would simply arbitrarily

say we go with the statistical plan, but, you know, these factors I think the agency appreciates were valuable in the study, and not to be ignored.

DR. HARRIS: Thank you. Yes.

DR. DeLAP: Just to add a couple of other comments to that, I think--and the company can comment on this if they need to--but I don't think that there were differences between us and the company that were meaningful in terms of the findings of the analyses that were done.

We spent more time describing certain analyses and the company spent more time describing other analyses, but I don't think there is any dispute that we have with what the company presented, and I think that the company understands where we were coming from with our analyses, and I don't think that they are off target either in terms of how the company sees them.

I think part of the issue here is that this is such a large database, and there are many different ways of looking at it, and I think we do feel, although we don't like to kind of violate statistical principles in the way we do things, I think we rarely get the opportunity to look at such large databases as this one, and we do feel that, you know, even if you haven't hit your primary statistical hypothesis, that doesn't mean we should look no further.

I think the company is interested and we are

interested in seeing, well, what is in there, and, you know, setting aside the purely statistical argument because, you know, this is the real world and we have to try and interpret all the information we have to the best of our ability. Again, we rarely get databases of this nature.

So, again, we are trying to explore again with the committee what is here, what is not here, and where do we need to go from here.

DR. GEIS: I think I can say from our point of view, we want to give the most medically meaningful interpretation, as well.

DR. HARRIS: Thank you, and we are aware of that, too.

DR. PINA: You know, in all fairness to the sponsor, if you look at the group that was on aspirin, they were probably on aspirin either because of a previous cardiovascular event or because they were considered high risk factors for future cardiovascular event, and I go back to Dr. Throckmorton's analysis, which I think is excellent, and you do see a trend to more cardiac events in the patients who have aspirin.

I am lumping together all the acute coronary syndromes because, as Steve well put it, they are all the same, just different gradations, whether it is unstable angina, myocardial infarction, or that myocardial infarction

causes death, it is the same underlying pathology, and there does seem to be a trend against this drug, but in all fairness, this may be the population who is already at risk, and that is why they are on aspirin.

So, for future trials, if the sponsor wants to think of future trials, I would do a trial in the population with cardiac history, who have had events, who are again the people with all these comorbidities and would be likely to come in with severe osteoarthritis and would need these drugs.

So, I think for future events, it raises a flag, but it also opens questions for the general use of these drugs.

DR. HARRIS: We may be straying into the next question, but Dr. Wofsy.

DR. WOFSY: I fear I am straying back to the last question. I need some clarification from Allan. When you were reviewing--because I shared, and I think many of us did, Dr. Wolfe's concern this morning, the sort of sense that one presentation says white, and the other presentation says black, and I think we do understand that actually that is not what is going on.

I, too, am looking for that answer, and I am about to cite some statistics with great trepidation to help me understand that, but they contradict something you said, and

I just wanted to double-check.

You cited in your answer to Dr. Wolfe a p-value of 0.45 for the primary comparison, am I remembering that right, in your notes, when you began to cite your notes?

DR. SAMPSON: I have Celebrex versus NSAIDs combined for POB, and that may be misdirected.

DR. WOFSY: I have, although we may be looking at different places, I thought the p-value was 0.09. In this particular case, I am reading it from the company report.

DR. SAMPSON: That is truncated at six months, I believe, and I was quoting from the annualized data. That is the difference. The company report again truncated everything at six months.

DR. WOFSY: And so if you go out to a year, you get 0.5 instead of 0.09?

DR. SAMPSON: I believe so. The FDA certainly could provide that exactly, but I think that is Dr. Goldkind's report.

DR. WOFSY: Then, you will spare me the rest of my comment.

DR. GOLDKIND: That is correct. The complicated ulcer for the entire study period, the overall p-value for combined NSAIDs was 0.45.

DR. HARRIS: I think we can move comfortably into Question No. 3. Are further studies warranted regarding

concomitant aspirin and COX-2 selective/traditional NSAIDs?

I guess we can start anywhere.

DR. NISSEN: I think there is a reality here, and that is we are facing an aging population that has both cardiovascular risk factors and arthritic disorders, and we are all seeing this more and more. We are going to see it more in the future.

We have an increasing number of trials including the very recently published primary prevention trial, which was in the Lancet just two weeks ago, showing individuals with even just one risk factor for coronary heart disease, a striking advantage in reduced cardiovascular morbidity and mortality with aspirin use, that we are probably going to treat increasing numbers of patients based upon these trials with prophylactic aspirin in the 81 mg to 162 mg dose.

Therefore, the likelihood that we are going to be mixing these two agents together is relatively high, and I think there is only one way to get an answer, and that is with a properly designed 2 by 2 factorial study where patients get a COX-2 inhibitor versus placebo with or without aspirin, and we find out what the both cardiovascular and gastrointestinal event rates are.

Now, that is a pretty good size study. You can do the power calculations. You can make it a little smaller if you don't try to do it at six months, if you try to go a

little bit longer with the trial to accumulate more events, but I think it would be very helpful to have that data. Whether it will ever happen or not, I have no idea, but it to me is the high road because it will clarify once and for all this interaction between the COX-2 and the COX-1 drugs, and we will find out a lot in such a study.

In many respects, one of the problems with the study that we have here now is it was relatively short term, and I think--I don't know what the average duration of therapy now is with patients with, say, osteoarthritis, but I am going to guess it is not six months, and so I think there is room for a longer term study, and a longer term study will answer some potentially important cardiovascular questions, as well.

DR. ELASHOFF: I just wanted to comment on the longer term study issue. It is not so much that they weren't intending to do a longer term study, but that people dropped out because of lack of efficacy and adverse events, so that before long, you didn't have any people in the trial, and I think no matter what you plan in the future, that is going to be a serious problem for making any long-term conclusion.

DR. HARRIS: That ultimately is one big limitation.

DR. WOFSY: I might just add to that, commenting

on the complexity of this issue, that if we did such a 2 by 2 study and came back several years later to analyze it, no doubt we would say about it that it should have been a head to head comparison between various COX-2 inhibitors because they look a little different, and it should have had some classic NSAID with and without aspirin arms.

I mean I agree with you, these are all questions we need answers to. they don't stop at the 2 by 2 study.

DR. PINA: I disagree that this should have to be a long-term study. I can see several very specific endpoints that would really answer some clinical questions.

For example, volume overload, renal dysfunction in a broad group of patients, you don't need a lot of time to see the endpoints, so if you ask some very specific questions, I don't think you have to do it very long term.

These are again older people. They have high frequency of events. They have high frequency of hospitalizations. You can probably pick up the events very early. I don't think you need to do anything very long term.

DR. CRYOR: I would agree because one of the observations that was clear from today's presentations was that many of these events occurred in the short term, in less than 30 days.

DR. M. WOLFE: The other question I would ask of

the people who designed these studies, would you want to stick to one dose of aspirin instead of making it less than a certain amount, just make it 81 mg period rather than confusing the issue.

DR. HARRIS: Dr. Pina, one question I realize is these studies, such as they were, were certainly extended for a while. You are answering that the answers would occur quickly. Why haven't they?

DR. PINA: But, again, I think this was a select population, and patients were probably, perhaps even at lower risk than I would like to see the population included. They excluded patients who had significant renal dysfunction. Most patients this age, as I said, have some renal dysfunction, so I would be more inclusive of patients to get reality, and they had a very high dropout rate.

I mean this is a pretty, pretty large dropout rate, so in other words, I would make it more inclusive, so that you get reality, pick shorter times and very, very distinct clinical endpoints which can be easily measured.

DR. HARRIS: Dr. Wolfe.

DR. M. WOLFE: I don't agree entirely from the gastroenterological point of view because these are cumulative events, and with time they occur. Your risk on day one is the same as the risk on day 365. So, you have to pick a time point. If you are going to annualize them, you

make it a year study.

DR. HARRIS: What I am going to ask is because I think what I understand the FDA requires is some advice about recommendation with respect to further studies, whether or not further studies might be warranted here.

Since I don't get a sense here, I will just ask everybody individually what their thoughts might be. I will start again with you, Dr. Wolfe.

DR. M. WOLFE: To avoid the confusion of two different NSAIDs, I would let the FDA decide a standard comparator NSAID, and compare--you pick the one you think is the gold standard for comparing, make sure everybody uses the same one from now on, where you are comparing your new COX-2--there will be other COX-2 inhibitors coming out. You are going to be facing this in the future.

Pick the one you want, so you compare apples with apples, although if you really want to compare COX-2 inhibitor to COX-2 inhibitor, it has to be done in the same study obviously. Pick the time point. Pick how long you would do the study, and also pick the dose of concomitant aspirin to help alleviate some of this confusion afterwards with regard to interpretation.

DR. HARRIS: So, you think that there should be other studies done?

DR. M. WOLFE: Yes, I think it is very unfortunate

the way it has worked out, because again, this is something which many of us expected the opposite result, and regardless of an explanation regarding endoscopic studies and the divergence, I still expected to see a difference in complicated ulcers.

We didn't, and because of that, no changes can be made in the present labeling. I think right now as it stands, these drugs are NSAIDs, and not a different class of drugs. This is easy for me to say, it is not my money, but I would like to see this study repeated in more standardized form.

Instead of saying less than so much aspirin, pick the dose, and divide it very clearly up which patients are on, which ones aren't, and pick one NSAID, and it will be the standard NSAID compared in the future.

DR. HARRIS: Dr. Pina.

DR. SAMPSON: Well, I am not in the habit of designing rheumatology trials, but from the cardiology trials, when a trial raises questions because of subgroup analysis or something that we weren't expecting, in this case I think aspirin has done for us, we go back and we focus on that specific question.

Why? Because it is going to have a wide applicability to the patient population that is going to be using these drugs, so I would go directly to the aspirin

question, I would use a comparator.

Again I agree that the FDA may want to choose ibuprofen because it is commonly used, because it is available over the counter, people use it whether you prescribe it or not.

It is being used extensively. Some of the others require prescription, but this is available in any drugstore in the form of Advil, Motrin, and whatever else you want.

Again, I would go back to very specific endpoints that become so problematic that we may not want to use these drugs in these patients. I mean I may go back and recommend Tylenol and heat and exercise if I think I am going to increase myocardial infarction rate or if I think I am going to increase hyperkalemia and edema, which is something that I deal with every day.

So, there are clinically meaningful endpoints that can be picked in a short term. It doesn't take a long time to see these.

DR. NISSEN: It seems to me we need two kinds of trials from my cardiovascular point of view. One, we need to know whether or not the COX-2 inhibitors with respect to thrombotic complications are neutral or worse than neutral, and I think there are some trends here that obviously concern me to some extent. So, that is one question.

Then, we have the question of the aspirin

interaction. Does addition of aspirin neutralize the pro-thrombotic potential, if that is, in fact, the case here, but does it do so at the cost of greatly increasing gastrointestinal side effects.

So, there are several issues not necessarily that can be decided in a single clinical trial. But I have to come back to the issue of global safety because I cannot, as a clinician, who sees patients, distinguish one serious adverse event from another.

From the point of view of the patient, a serious adverse event is a serious adverse event. I mean, you know, it doesn't really matter if you end up in ICU with an infarction or with a bleeding ulcer. So, I think we have to look at the total serious adverse event rates both with and without aspirin for this class of drugs, and try to find out whether there is an advantage or not an advantage, and that probably means I recognize that there are other comparators involved, but it does mean some kind of a factorial design to try to answer the question in a really scientific and a rigorous fashion.

DR. HARRIS: Ms. McBrair.

MS. McBRAIR: I think because of the aging population and the increase we are going to see in comorbidity, it definitely does need more study and evaluation.

DR. WOFSY: I think important questions have been raised here. I won't repeat the things that have been said by others, but certainly our unanswered questions regarding these agents that are very important including, as has been pointed out by Dr. Wolfe, whether this is an aberration and we were all right in expecting a different result, or whether this is real.

So, the fundamental question that was asked here is important to answer, it was important to answer, and it is still important to answer, and the questions that were raised in the course of doing this are important, so there has been sort of a factorial growth of interesting questions.

I would just sort of make one side point. It isn't our purpose here, and we couldn't do it in a group this size anyway, to design specific studies, but I would have some caution about the suggestion that has been made that the FDA should pick one comparator and everybody should use it, because if there is any evidence coming out of this, it may be different if you pick one comparator than if you pick another, and we have no idea which one is the right one.

I don't have a solution to that problem, but I do believe that it is not going to be a simple question to answer what the design should be and what the comparison

should be.

DR. CALLAHAN: I agree with Dr. Wofsy and the other speakers that important questions have been raised, and I would like to reiterate I do not think there is a gold standard and that the FDA should pick a gold standard to ever compare against.

DR. HARRIS: I will also agree with what is being said. Indeed, there seem to be more questions raised than some answers here. Of course, bearing in mind that the issue is that we are faced with large numbers of patients who are elderly, who are going to be on low dose aspirin anyway, and the issue is whether or not additional studies, what would really sway me and what does make me think that there may need to be some more studies is whether or not the COX-2 inhibitors are actually posing some degree of cardiac toxicity, and then, in fact, this whole issue of low dose aspirin becomes very important indeed.

DR. WILLIAMS: We have talked about a lot of different studies, and I agree with what has been said. In specific response to Question No. 3, aspirin has been shown to be a confounder in safety studies, so I do think we need to have better clarification of it.

DR. SAMPSON: Actually, I have been sitting here pondering. It is difficult to think about what exactly future studies are warranted. It would depend on the goals

that one would have in those studies, and the two issues that came up here is the GI safety and the cardiovascular safety, and I also hear Dr. Nissen, the combined safety.

It is not so clear to me that they need to do more studies in terms of the GI. They have a lot of answers here other than the paradox of the ibuprofen and the aspirin combination, which I don't know what to make of that.

In terms of the cardiovascular safety and what we are going to hear tomorrow, that is a very intriguing question and clearly, I think more studies are going to be needed to deal with that, and again, in the context of tomorrow, both in an OA and an RA population.

DR. ELASHOFF: It does seem that there are a number of issues which it would be important to know more about. I think it would be quite challenging to design a study which would address those questions effectively, and whatever the design is, I expect that it, like this trial, will raise more questions than it answers.

DR. HARRELL: Sort of along the lines of Dr. Nissen, I think the need for a future study that ferrets out this aspirin interaction is proportional to whether a net positive risk-benefit equation can be demonstrated for all comers, which I haven't seen yet.

DR. HARRIS: Dr. Cryor, you notice that we have been ignoring you. Of course, you are not a voting member,

but we would appreciate any comment you would want to make.

DR. CRYOR: I have not taken it personally actually, I have enjoyed the break.

Again, I do think that the data is very interesting and hypothesis and generating, and future studies would be interesting, but I would pose the question just a little differently with respect to future studies, and that would be future studies along the lines of newer antithrombotic agents that might actually replace the efficacy of aspirin as an antithrombotic agent because I think much of what we are seeing in the gastrointestinal tract with respect to outcomes is there and is going to be a fixed consequence of low doses of aspirin.

DR. HARRIS: Thank you.

DR. M. WOLFE: I actually was going to say something about the safety. Again, we are concentrating on aspirin a lot, and we should because it is used a lot. On the other hand, these drugs have to stand on their own, too, and we must consider them on their own.

Also, this is not going to be a static situation. Although I can't predict what is going to happen in the future, I know what is being developed, and the future may be a nitrosylated aspirin for everybody instead, which may take away the disadvantage that regular aspirin has.

So, again these drugs must stand on their own. I

want to come back again to the idea of the standardized NSAID comparator. We are looking at individual drugs, which we must do, but the clinicians out there and individuals out there taking these drugs will look as a CLASS effect, and unless a standardized format is picked, there is still going to be this confusion always arising.

Now, I can't speak for Pharmacia, what was picked was picked, but my speculation is ibuprofen is used in this country and diclofenac is used in Europe a lot, and diclofenac is not used here that much.

Why don't you again make a suggestion? It is not unusual for FDA to have suggestions regarding studies. Have you suggested comparator and combine them? If you don't want one drug, have two drugs or three drugs that are used, and then combine them for the analysis.

I am not going to back off on that. I really think you are going to have more confusion in the future if you have different comparator drugs because you can't tell if it's a comparator or if it's the drug itself being tested.

The last thing about the aspirin-ibuprofen, I hate to tell you this, but the statistics aren't perfect, and I think it is an aberration that somehow there was something that took place, and it's a type 1 error of some sort, and I don't know what it means.

DR. SAMPSON: The p-value is 0.15. It wasn't even a type 1 error.

DR. M. WOLFE: It's an aberration of some sort.

DR. HARRIS: I will leave the issue of the standardized comparator to another session of the FDA later on, not now.

Let's move to the fourth question. Considering the results of the CLASS trial, do the current NSAID related target organs for toxicity in the current NSAID template remain applicable? This is GI, renal/fluid retention, hepatic and skin. It is open for discussion.

DR. ELASHOFF: The only thing that I heard that sounded like FDA saw an additional problem in, the Celebrex versus the NSAIDs with skin, but I don't know, I haven't read this, whether that is already totally covered there, so it is not an issue.

DR. HARRIS: I think it is. Would somebody from the FDA comment?

DR. WITTER: Could you clarify what you mean by it is covered?

DR. ELASHOFF: In terms of what is already said in the template.

DR. WITTER: Those events are already in the existing label.

DR. ELASHOFF: I didn't pay a lot of attention to

that, but it looked to me as if those were worse than the NSAIDs. Would we need to make a comment from that point of view?

DR. WITTER: The current labeling notes that one of the more problematic areas with this particular compound is the skin.

DR. WILLIAMS: I didn't hear anything today that would make a difference either way in the current template.

DR. HARRIS: Anybody else? Did you hear anything different today that would change?

DR. NISSEN: I am not sure if I fully understand the template here, but with respect to platelet effects, the template looks at the CLASS together, and the question is do we need to say something different about platelet effects for the COX-2 inhibitors in the labeling.

In other words, the issue of cardioprotective effects.

DR. HARRIS: Let's clarify template, you know, just exactly that. I presume it's the label, and the question is, you know, and then perhaps they are referring to the question with respect to platelets.

DR. WITTER: The template, as I indicated earlier I think, is best viewed as a general structure for when the label is written. In terms of the comments relating to platelet or aspirin co-use and any thoughts that you might

have, that's what we are looking for today.

I think what we are looking for, anything that you think should be changed because of this data, and really any aspect of the template. I think we focused on the ones that we have here, but should you have any other issues, we would certainly like to hear them, too.

DR. WILLIAMS: After that specific comment, I may make one change, and that is, for those that are specific COX-2 inhibitors, you may wish to add the fact that aspirin may negate some or add additional complications, that it will negate the benefit of the platelet lack of inhibition.

DR. HARRIS: Can I ask, is there not wording that might be similar to that with respect to the concomitant use of low dose aspirin or any other nonsteroidals?

DR. PINA: In the template here, there is one statements that says, "All drugs which inhibit the biosynthesis of prostaglandins may interfere with the extent with platelet function and vascular responses to bleeding."

I would like to see something more specific, that this is not meant to take the place of the cardioprotective effects of anti-platelet use with aspirin. I would like to see the hyperkalemia added to the fluid retention right after the words "heart failure." Where there is the fluid retention and edema, I would like to see the hyperkalemia added, and I would like to see the hyperkalemia added to the

little paragraph here on ACE inhibitors.

DR. WITTER: You are referring specifically to Celebrex?

DR. ELASHOFF: Yes.

DR. DeLAP: I think as Jim might have been about to say, the Celebrex label, of course, is customized to significant degree from the template, and we do have with products that we have approved recently in the COX-2 arena. We have certainly included a statement that these are not to be used as a substitute for aspirin for the cardiovascular benefits of aspirin.

There also is a statement-- I have to go back and look at it again--about that you can expect more toxicity if you combine with aspirin or other nonsteroidal agents, but I have forgotten the exact terminology we used.

DR. HARRIS: Excuse me. Just before, just for clarification, so there is a statement with respect to increased toxicity with core use of aspirin, concomitant use of aspirin.

DR. WITTER: In the section on use with aspirin it discusses endoscopic ulcer, and the rate appeared to be higher in aspirin users than in non-users, for example.

DR. M. WOLFE: With regard to the PI, is it merely a statement saying these are not aspirin substitutes, and in light of getting ahead of ourselves, tomorrow's discussion,

should it be more than just a simple statement, should it be a bold statement of some sort saying these are not aspirin substitutes?

DR. WITTER: Well, I think that it is an important message. I think we have to make sure the message gets across. The issue of exactly, you know, where you put something in the labeling or what you bold or those kinds of things are very complicated kinds of issues that we still grapple with because we want to make sure that the things that people need to know are communicated certainly.

But again, to answer the original question, that thought that these products, Celebrex is not a product that you can use as a substitute for aspirin for the cardiovascular effects of aspirin because it doesn't have the same platelet effects. That is expressed in the current labeling.

DR. CRYOR: From the GI perspective with respect to celecoxib labeling, one thing you may want to consider is a broadening of the range of the specified incidences of ulcers that can be expected to occur with NSAIDs at six months and at a year.

Although we didn't find any statistically significant difference with the primary endpoint, it does highlight that there may be a broader range than suggested by current labeling.

DR. HARRIS: Is that generally agreed, the last suggestion made by Dr. Cryor? Any other comment? Okay.

The last question to ask is that, of course, there is a degree of sensitivity with respect to possible cardiac effects, and presumably this is going to occur, I guess, more tomorrow, but based on where we are with respect to the template, I presume that there is a comfort level leaving things as they are with respect to Celebrex.

DR. PINA: I would agree except again to emphasize the points that we just made about the non-substitute for platelet inhibition by aspirin and the other hypertension, myocardial infarction, edema, and hyperkalemia, which are all meaningful cardiac problems to the clinician.

DR. WITTER: Can I just clarify in the label, it does mention--this is under the section of metabolic and nutritional--it does mention hypokalemia, so I was remembering something about that, and that is what it was.

DR. HARRIS: Hypo or hyper?

DR. WITTER: Hypo.

DR. PINA: But you need to add the hyper to the ACE inhibitor area because a lot of people will go directly and only read that little section on ACE inhibitor use.

DR. NISSEN: I am not entirely comfortable, and let me see if I can share with you the discomfort. It is hard for me to separate our discussions today from our

discussions tomorrow because we have got a lot of data here to look at, and the general class of drugs of COX-2 inhibitors, we have a question here, and the question is in comparison to not giving aspirin, are they neutral with respect to thrombotic events or are they worse than neutral.

You go back to Fitzgerald's hypothesis of this balance between thromboxine and prostacycline, and I don't yet know the answer to that question of whether they are neutral or worse than neutral.

In other words, do they simply lack the aspirin benefit or are they worse than not giving aspirin at all. That wasn't really the design or intention of either of the trials we are going to look at, but we have to also understand that this was for a given population.

What is going to happen if we give these agents to patient populations that have a higher risk profile for cardiovascular events? Are we going to see something happen here that wasn't anticipated?

I would not be doing justice to my coming here to join you if I didn't tell you that I have got a certain discomfort level about this whole problem and what to do about it. This was a pretty low risk group of patients that were studied, and the question is are we giving these agents to patients at higher cardiovascular risk, and if we do so, will we see something that we wished we didn't see, and I

don't know the answer to that.

DR. M. WOLFE: I am reading the PDR right here. Yes, you have the information regarding that celecoxib is not a substitute for aspirin, and right below it is that there is a problem with interaction with fluconazole, which is more important. I think that aspirin nonsubstitution has to stand out more until proven otherwise.

DR. WILLIAMS: I agree with some of your discomfort, but I don't think we have any data to change the label with.

DR. HARRIS: And that is the issue I mean for today. Today is today, and whether or not you have any data to change the label, and that is really the question.

DR. HARRELL: We have some data, but the confidence intervals are just very wide, but I am wondering if we still shouldn't put those confidence intervals in there.

DR. HARRIS: I think we do have a consensus that considering the results of the CLASS trial, do the current NSAID-related target organs for toxicity in the current NSAID template remain applicable? The answer is largely yes. There were some additional comments made with respect to low dose aspirin and with respect to platelets.

Are there any other closing comments that anyone has a burning desire to say?

Well, thank you very much. Session closed.

[Whereupon, at 3:25 p.m., the proceedings were recessed, to resume on Thursday, February 8, 2001.]

CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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